IMTS # 8956

**MEETING MINUTES**

Docket #: 80N-0042 and 81N-0033
Topic: Listerine with Fluoride
Sponsor: Pfizer Inc.

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| Meeting Request Date: | April 16, 2002 |
| Meeting Package Submission: | June 27, 2002 |
| Meeting Date: | August 27, 2002 |

**Background**

The Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee has recommended that the fixed combination of essential oils found in Listerine be placed in Category I (safe and effective) for the control of plaque and gingivitis. The Advance Notice of Proposed Rulemaking (ANPR) for Antiplaque/Antigingivitis Drug Products is pending publication. Although the Panel stated that combining an anticaries agent with an antigingivitis agent is a logical combination, no specific products or data were reviewed. Pfizer is proposing a product containing Listerine combined with sodium fluoride and, after completion of the appropriate studies, plans to submit a citizen's petition to amend the Anticaries Final Rule to include this product as an anticaries/antigingivitis rinse.

**Meeting Attendees**

FDA Office of Drug Evaluation V

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| Jonca Bull, M.D. | Office Director |

Division of OTC Drug Products

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| Charles Ganley, M.D. | Division Director |
| Debbie Lumpkins | Team Leader |
| Robert Sherman | IDS Reviewer |
| Elaine Abraham, R.Ph. | Project Manager |
| Gerald Rachanow, P.D., J.D. | Regulatory Counsel |

Division of Dermatology and Dental Drug Products

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|---|---|
| John Kelsey, D.D.S., M.B.A. | Dental Team Leader |
| Fred Hyman, D.D.S., M.P.H | Dental Reviewer |

81N-0033 MM 9

Office of Compliance

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| Robert Eshelman | Consumer Safety Officer |

Office of Biometrics

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| Shiowjen Lee, Ph.D. | Statistician |

Pfizer, Inc.

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| Michael Barnett, D.D.S | Consultant |
| Thierry Bilbault, Ph.D. | Director, Product Development |
| D. Scott Harper, Ph.D. | Section Director, Oral Care Technology Development |
| Donald Jantzen, Ph.D. | |
| Robert Kohler | Regulatory Consultant |
| Lori Kumar, Ph.D. | Senior Director, Clinical & Product Development-Oral Care R&D |
| Michael Lynch, D.M.D., Ph.D. | Director, Clinical Research-Oral Care |
| Dawn M. Parkin | Manager, Regulatory Affairs |
| Mei-Miau Wu, Ph.D. | Manager, Statistics |

Other Attendees

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| Parker Holmes | GlaxoSmithKline |
| Mark Barry | Cumberland Swan |
| Michel Marcoux | The Tan Sheet |
| Greg Collier | Procter & Gamble |
| Stephen McClanahan | Procter & Gamble |

**Meeting Minutes**

Dr. Barnett briefly reviewed the studies submitted by Pfizer to support the use of Listerine with Fluoride: A 2-week intraoral appliance (IOA) study and a 2-week experimental gingivitis study. Dr. Barnett stated that the IOA study showed comparable effectiveness between the Listerine with Fluoride product and the monographed sodium fluoride rinse. The experimental gingivitis study examined the impact of fluoride on the antigingivitis effectiveness of Listerine. The conclusions from this study were that the addition of sodium fluoride did not affect the antigingivitis effectiveness of the fixed combination of essential oils. Dr. Barnett stated that this result is consistent with the published literature showing that sodium fluoride is effective against caries with no impact on gingivitis.

The following questions were provided by Pfizer and discussed:

1. ***Are there any comments regarding the suggested monograph changes to support the formulation?***

   Pfizer proposed the addition of a new Anticaries active ingredient section to be added to 21 CFR 355.10(a)(3), between current (ii) and (iii) as follows:

   > An aqueous solution of sodium fluoride acidulated with a mixture of benzoic acid and sodium benzoate to a pH of approximately 4.2, which yields an effective fluoride ion concentration of 0.01 percent.

   FDA responded that this change to the monograph should be placed in a new section of the monograph, 21 CFR 355.20, in which combination products will be discussed. The statement should include the essential oils as well in this definition, as the benzoic acid/benzoate solution was not tested alone and there is no intention to market benzoic acid/benzoate alone without the essential oils. The current 21 CFR 355.20 would be shifted to 21 CFR 355.30.

   FDA asked whether Pfizer plans to refer to the active ingredient on the label as sodium fluoride or acidulated sodium fluoride. Although Pfizer has no objection to either choice, the company prefers that sodium fluoride be listed as the active ingredient.

   Pfizer pointed out that the formula used in the study has the same ingredients as the Listerine product reviewed by the Panel, but the alcohol level is lower. FDA stated that when Pfizer is ready to petition for the inclusion of Listerine with Fluoride in the monograph, the formula studied should be the one that is included in the monograph.

   Pfizer also proposed the addition of a new Directions for Use section to be added to 21CFR 355.50(d)(2) after current (ii) as follows:

   > For acidulated sodium fluoride solution containing 0.01 percent fluoride ion identified in 355.10(a)(3)(TBD). Adults and children 12 years or older: Use twice a day morning and night after brushing your teeth with toothpaste. Rinse full strength for 30 seconds with 20 ml (2/3 fluid ounce or 4 teaspoonfuls). Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing.

   FDA stated that this proposed change should be placed in a new section of the monograph, 21 CFR 355.60, in which directions for use of combination products will be included.

   FDA questioned certain terminology used by Pfizer in the directions that differs from the monograph. The proposed labeling uses the phrase "rinse" in place of

"vigorously swish". Also, the phrase "morning and night" for dosing frequency is used rather than "twice a day" as in the monograph. Pfizer explained that the wording was taken from the current Listerine labeling, but they would be amenable to changing it to agree with the monograph. The age requirements were also discussed. The monograph allows use down to 6 years of age. The Listerine product lists the age range as 12 and older. Pfizer explained again, that this is consistent with current Listerine labeling, but could be changed to agree with the monograph.

The Listerine with Fluoride combination product affects two rulemakings - anticaries and antiplaque/antigingivitis. It is likely that the ANPR for Antiplaque/Antigingivitis Drug Products will be published by the time the 6-month study planned by Pfizer is completed. Because that rulemaking is only at the ANPR stage and the anticaries monograph is final, the FDA needs to propose to amend the anticaries monograph, which does not provide for such a combination product, before marketing of the new product can occur. Marketing could begin after the comment period closes and a second notice (enforcement policy) allowing the marketing of the combination or a final amendment is published.

***IOA and experimental gingivitis studies***

Before proceeding to FDA's comments on the 6-month gingivitis study, Pfizer asked if the two 2-week studies submitted would be sufficient support of effectiveness so that the 6-month study would not be necessary.

FDA responded that the 6-month study is the pivotal trial and the other studies are supportive. FDA provided the following comments on the 2-week studies.

- Intraoral Appliance Study - As per the earlier agreement with the agency, the IOA model study was conducted to support the addition of Listerine to the fluoride mouthrinse does not negatively impact on fluoride's ability to help prevent demineralization of enamel. Assuming that the statistical analyses are sound, the results met the prespecified requirements for "at least as good as" the positive control and superior to negative control by 10% Surface Microhardness (SMH) units.

- Experimental Gingivitis Study - The Experimental Gingivitis trial is supportive, but has one major problem. The Gingival Index (GI) reduction was 14.8%, which did not meet the generally accepted guidelines of 20% overall reduction.

2. ***Are the proposed treatment cells for the Six-Month Gingivitis Study acceptable?***

3. ***Is the proposed statistical plan for the Six-Month Gingivitis Study acceptable?***

Questions 2 and 3 were answered together by FDA with the following comments:

- Pfizer proposes that the current primary outcome meet the provision that both the plaque and gingival indexes in the test product, essential oil-containing mouthrinse with fluoride, are "at least as good as" the positive control, essential oil-containing mouthrinse without fluoride, and that they are significantly better than the hydroalcohol (vehicle) control. The proposed testing requires a statistically significant improvement in the GI of the test product over the vehicle; generally accepted guidelines also require a 20% difference in magnitude to fulfill clinical significance.

- The difference of 10% between negative control and active in the sample size calculation should be clarified. As discussed above, Pfizer needs to ensure that the sample size calculation also satisfies the 20% difference criterion.

- The intent-to-treat (ITT) analysis should be primary for superiority comparison. The FDA recommends defining the ITT population as all randomized subjects who are dispensed the study drug, regardless of having any post-baseline or evaluable data. For the non-inferiority comparison, it is recommended that both ITT and per-protocol (PP) analyses be submitted. The PP population should be defined in the protocol.

- Subgroup efficacy analysis (by demographics and baseline characteristics) should be planned in the trial.

- The protocol (page 24) states that any changes in the planned statistical methods would be documented in the integrated clinical/statistical report. The primary analysis methods should be pre-specified in the protocol to obtain FDA concurrence. It is difficult to make judgments concerning statistical methodologies that are not pre-specified in the protocol, as this would be a review issue.

- Since the study is a randomized trial, the patient's treatment allocation should be generated prior to the initiation of the trial. Patient demographic data should include the time/date of enrollment for each individual.

- Generally, for one pivotal trial to be acceptable for regulatory purposes, it should be a robust, multicenter trial. The proposed study is scheduled to take place in Ontario, Canada as a single center study. The trial should be multicenter (3 centers but can have one primary investigator).

- The proposed analysis for the primary and the secondary efficacy endpoints based on the ANCOVA method is acceptable. As it is recommended that a multicenter trial be conducted, "center" effect should also be included in the ANCOVA. The treatment-by-center and treatment-by-smoking status interaction effect should be tested. The interaction effect should be tested at a significance level of 0.10 instead of 0.05.

- In the currently proposed protocol, individuals are excluded who 1) are pregnant, 2) have uncontrolled diabetes, 3) have orthodontic appliances or partial dentures, 4) have taken antibiotics within the past month or 5) have oral piercing. These individuals are being eliminated due to either the difficulty of recording accurate and reliable measurements on them, or due to the confounding that their condition has on gingivitis. Nonetheless, Pfizer is excluding individuals in an OTC evaluation who will have access to Listerine, and detailed labeling that would discuss their exclusion is usually not used for OTC drug products. Pfizer should reconsider inclusion of these subjects, or explain why it is crucial to exclude them.

- Pfizer should clarify a statement under Section 7.4 of the protocol (page 9 of Attachment 3) in which it is stated that "The examiner will not have access to the case report forms until the completion of the examinations."

**Action Items:**

1. Pfizer will submit a revised 6-month gingivitis protocol.

2. FDA will provide comments on the revisions.

Elaine Abraham
Minutes Preparer

Charles Ganley, M.D.
Concurrence

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: 10/4/02

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 80N-0042 81N-0033

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☑ This material should be cross-referenced to Comment No. LET 051 (80N-0042)
LET 054 (81N-0033)

Charles J. Ganley, M.D.

Attachment